The first death I witnessed in medical school 35 years ago was avoidable. The patient had a cardiac arrest during an otherwise routine angiogram. The anesthesia resident on the crash team intubated the patient and managed the airway while the cardiologists ran the code. Unfortunately, the anesthesia machine in the angiography suite was different from those the resident normally used in the main operating room; the knobs were reversed and labeled differently. When he reached over to turn on the oxygen while holding the endotracheal tube in place before it was taped, the resident delivered pure nitrous oxide instead. By the time the error was recognized, it was too late.

People make mistakes. Today’s anesthesia machines are designed to prevent human errors caused by distraction, confusion, or poor training. Knobs, labels, and connectors are now standardized globally, and mechanical interlocks prevent the delivery of pure anesthetic agent without oxygen. The remarkable safety records of modern commercial aviation and anesthesia are largely due to human factors research—the careful, systematic study of how critical systems work and fail in the real world. In medicine as in aviation, the weak link almost always turns out to be the human being.

The delivery of topical ophthalmic medications has changed little since miotics were introduced to treat glaucoma in the late-1800s: An ophthalmologist prescribes a medication; the patient purchases a dropper bottle labeled with printed instructions; the patient or family member is expected to administer the medication to the correct eye(s) at the appropriate interval. What could possibly go wrong? Indeed.

Viewed as a system, the workflow from the ophthalmologist’s prescription to the patient’s eye(s) has many discrete points of failure, most of which involve human behavior. We now prevent most of the human errors originating among health care providers—electronic prescribing replaces illegible handwriting, and decision-support software provides alerts about allergies and drug–drug or disease–drug interactions. The pharmacist no longer must transcribe the electronically received prescription to generate a label (another source of error) and can even translate instructions and educational material into the patient’s native language with the click of a mouse.

But what happens when the patient brings the dropper bottle home? And how, when the patient returns to our office, do we reassure ourselves that the patient is in fact taking the correct drugs correctly? This aspect of end-user behavior has for the most part been a black box. In 1983 an informal agreement among the pharmaceutical industry, the American Academy of Ophthalmology, and the US Food and Drug Administration led to ophthalmic medications being packaged with loosely standardized colors on bottle caps and labels to represent different classes of medications. A yellow cap usually represents a beta-blocker, a teal cap represents a prostaglandin analogue, a pink (or white!) cap represents a steroid, and so on.

Consider the target audience—patients with ophthalmic disease who often have decreased or impaired visual acuity, contrast sensitivity, and color perception. In this issue of Ophthalmology, 2 articles (see pages 2373 and 2577) illustrate the problem that arises when we depend on color alone to communicate with our patients about their medication regimen. Marando et al surveyed a convenience sample of 126 patients and found that to keep their glaucoma medications straight, 65% of the patients depended on cap color—far more than printed material such as medication name (18%) or information printed on the box; most supplemented cap color with other indicators such as bottle shape (48%) or even stored medications in different locations to distinguish among them.

Dave et al asked a convenience sample of 100 patients with glaucoma to provide a description of the cap color of 11 distinct medications. The patients provided 102 unique descriptions of these colors—4 of the medications had less than 15% agreement between what the patient described and what the physician understood the medication to be. Considering that the authors excluded patients with acuities <20/400, real-world performance is probably worse. Dependence on correct color discrimination to determine what medications patients are actually using almost certainly results in preventable errors.

This problem will only get worse. New classes of topical agents will be introduced in the next few years along with new combination products. As patents expire, we will see generic versions manufactured by companies not part of the informal color cap agreement between the American Academy of Ophthalmology and the Food and Drug Administration. Our patients already receive drugs from different manufacturers each time they go to the pharmacy and they are confused. Figure 1A shows versions of topical beta-blockers available to my hospital’s pharmacy in mid-2015. Look at the packaging from the standpoint of a visually impaired patient who takes home a different bottle after each trip to the pharmacy. Note the varying bottle designs and lack of color consistency in the labels and caps
for similar medications, including combination products. Both betaxolol (a beta-blocker) and dorzolamide-timolol fixed combination are packaged by 1 generic manufacturer in identical bottles with dark blue caps. Confusing packaging is even more common outside the United States. In Indonesia, timolol and pilocarpine are both packaged in identical green labeled and capped bottles (Fig 1B), and in Vietnam, a variety of medications are all packaged with white labels and caps (Fig 1C).

The American Academy of Ophthalmology policy statement on color codes for topical ocular medications, recently updated to accommodate new products, is, sadly, not enough. Dependence on color discrimination alone for patients to differentiate among medications fails basic principles of human factors research and product design. We should follow the examples of human factors research in aviation and anesthesia to design our drug-delivery systems with the visually impaired and confused end user in mind.

For example, we could add tactile clues and fail-safe interlocks to avoid human drug-delivery errors. The next time you fly in a commercial aircraft, take a peek in the cockpit. The levers controlling flaps and speed brake each have different shape knobs that reflect their function, and the landing gear lever’s knob is even shaped like a wheel! This is not done to be cute, it is done so that the pilot can reach over to adjust things quickly without a second glance in a moment of stress. In a similar manner, different classes of topical medications could and should have caps with tactile clues based on the class or frequency of dosing. A once-daily medication could have a round cap, a thrice-daily medication could have a triangular-shaped cap, and so on. This standardized iconography (shape, color) would appear prominently on the label and box. The same shape would be debossed (raised) on the bottle so that the patient can feel the cap and bottle to be reassured that he is using the correct medication correctly even if he cannot read the label or if the label has rubbed off.

What if the patient puts a cap back on the wrong bottle? I emphasize to my patients that they should bring their medications with them to every visit so that we are “always

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**Figure 1.** A, Commercial packaging of topical beta-blockers (both solution and gel) obtained from a California drug wholesaler in July 2015. The yellow caps vary widely, and some are white with a yellow sticker. Some labels have no yellow content at all or have prominent design elements in red. Text is tiny and requires excellent near visual acuity to read. On the left, a product containing betaxolol hydrochloride and another containing a combination of timolol and dorzolamide are both packaged with identical dark blue caps. B, Commercial packaging of both pilocarpine and timolol in Indonesia. Note that both bottles are identical in appearance with green labels and caps. The only differentiator is the text. C, Commercial packaging of some glaucoma medications available at the Vietnam National Institute of Ophthalmology hospital pharmacy in Hanoi, Vietnam, June 2015. Note that all have white caps.
Cap switching is remarkably common. Here too, we can follow the lead of anesthesia, where the connectors to refill anesthesia machines have physical interlocks so that liquids cannot be poured into the wrong anesthetic vaporizer. For eye drops, caps for different classes of medications could each be threaded in a unique, standardized manner so that the cap for a topical steroid cannot be screwed onto a bottle containing a prostaglandin analogue.

The International Organization for Standardization (ISO) (www.iso.org) is an international nongovernmental organization that develops and publishes standards across all aspects of technology and business, including medicine. If you go to any hospital in the world, you will notice that blood-collection tubes are color coded the same everywhere. Why? It is an ISO standard (6710:1995). The agent-specific filling systems for anesthetic machines mentioned above? Another ISO standard (5360:2012).

The ISO standards come about when the many stakeholders in a given field work together to propose, generate, discuss, and refine a global standard. The ISO process can be initiated not only by industry but also by end-users such as physicians and patients, who see a glaring need for standardization.

Ophthalmic drug delivery is such a need. The lowly eye-dropper bottle has not been fundamentally redesigned since the 1800s beyond the shift to plastic 50 years ago. It has never been subjected to the critical analysis that is the hallmark of modern human factors research. It is time for patients, physicians, regulators, and industry to work together through the ISO process to develop a global standard for how ophthalmic drugs are packaged and labeled. Only when we are all on the same page can we communicate in a common language and be certain that our patients are taking their medications correctly.

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